Investigation of lipopolysaccharide (LPS) administration by intraperitoneal (i.p.) injection and intracerebroventricular (i.c.v) infusion as mouse models of neuroinflammation

Transpharmation
Science that translates into results

Introduction

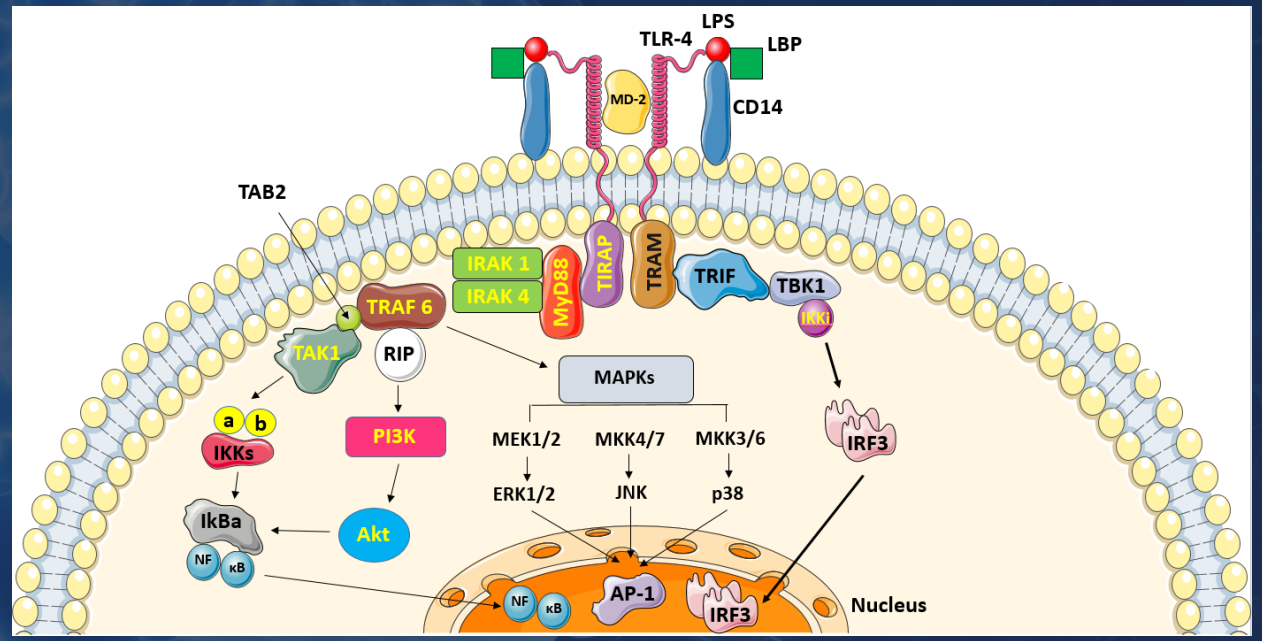
- Neuroinflammation has been linked to the pathogenesis of multiple neurodegenerative and psychiatric disorders.

- LPS (lipopolysaccharide) is an outer membrane component of gram-negative bacteria that has been used to model neuroinflammation, yet few studies have compared peripheral and central cytokine expression.

Aim:

- To directly compare the inflammatory response induced by LPS through i.p. and i.c.v. administration in both the central nervous system and the periphery

- To investigate the effect of sub-chronic and acute minocycline as well as acute dexamethasone pre-treatment on i.p. LPS-induced inflammation



TLR-4 Pathway

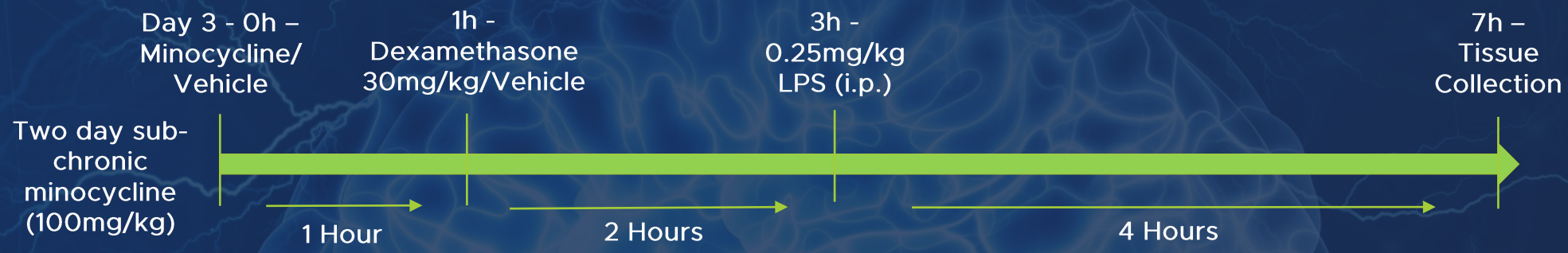
Methods – Experiment 1 and 2

Group	Treatment	Concentration	Route	Tissue Collection N=6
1	Saline		i.p.	4 Hours
2	LPS	0.1 mg/kg	i.p.	4 Hours
3	LPS	0.25mg/kg	i.p.	4 Hours
4	LPS	0.5mg/kg	i.p.	4 Hours

Group	Treatment	Concentration	Route	Tissue Collection N=4
1	aCSF		i.c.v.	4 Hours
2	LPS	1µg/mouse	i.c.v.	4 Hours
3	LPS	5µg/mouse	i.c.v.	4 Hours
4	LPS	20µg/mouse	i.c.v.	4 Hours

- 4 hour i.p. or i.c.v. LPS
- Brain and trunk blood collected
- TNF-α, IL-6, IL-1β and CCL2, CCL3, CCL4 measured in plasma and left hemisphere via Meso Scale Discovery platform

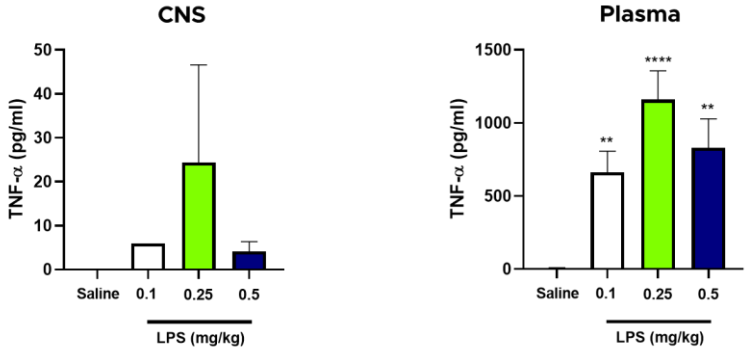
Methods – Experiment 3



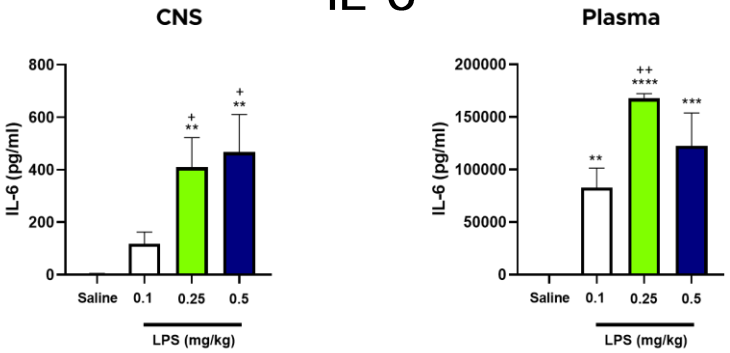
- Minocycline administered sub-chronically and acutely by *intraperitoneal injection (i.p.)*
- Dexamethasone administered acutely *per os (p.o.)*
- LPS administered i.p. (0.25mg/kg)
- Brain and trunk blood collected
- TNF-α, IL-6, IL-1β and CCL2, CCL3, CCL4 measured in plasma and left hemisphere via Meso Scale Discovery platform

Results 1

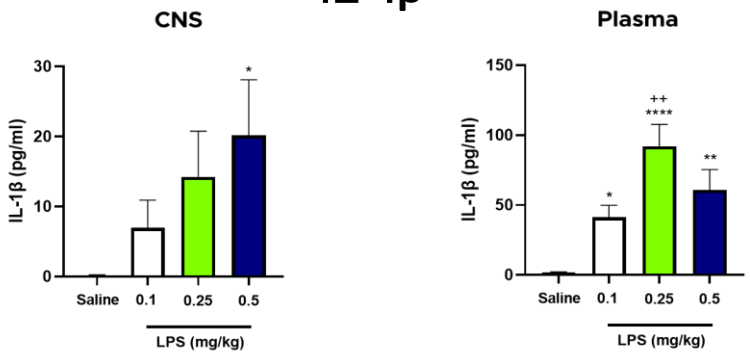
TNF-α



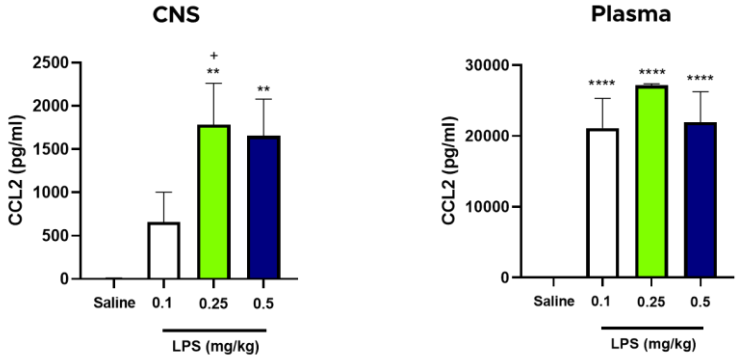
IL-6



IL-1β



CCL2



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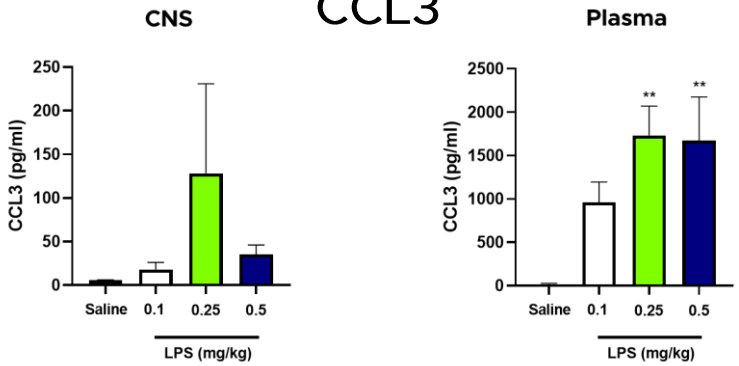

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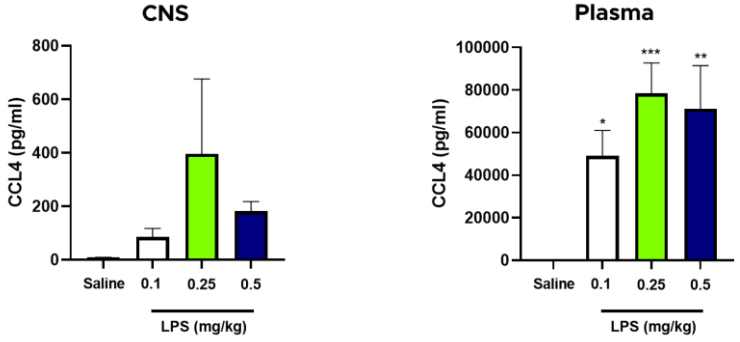
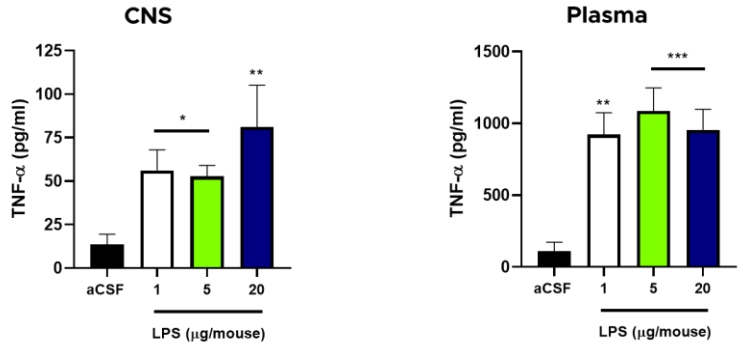


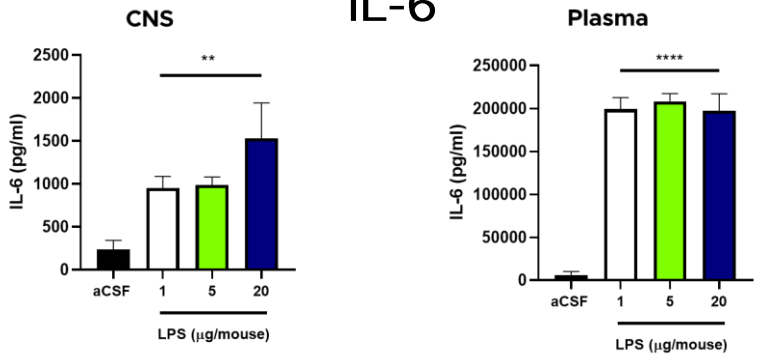
n=5-6 per group. One-way ANOVA (P<0.05); Fisher's LSD. Values expressed as protein concentration (pg/ml). Data presented as Mean ± SEM.

Results 2

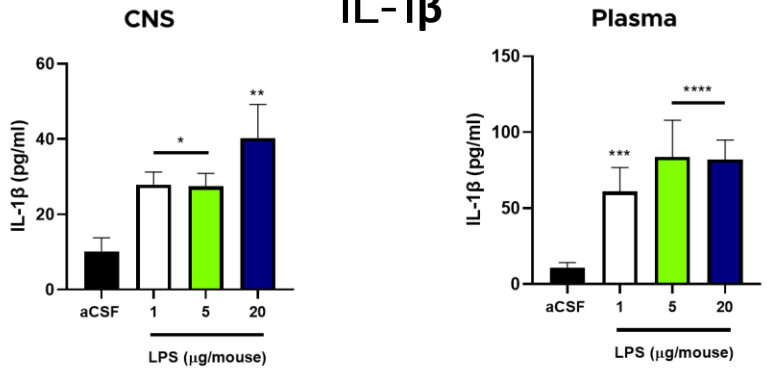
TNF-α



IL-6



IL-1β



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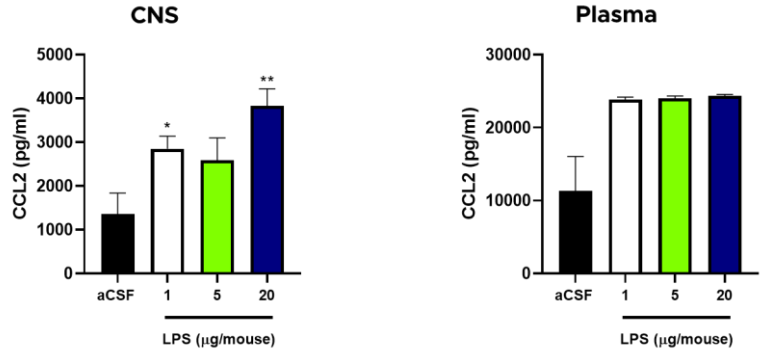

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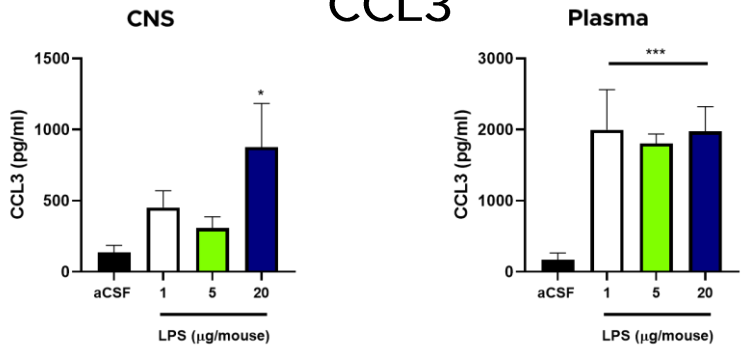

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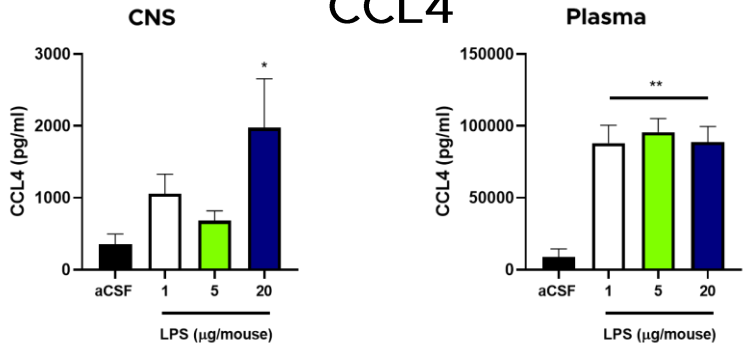
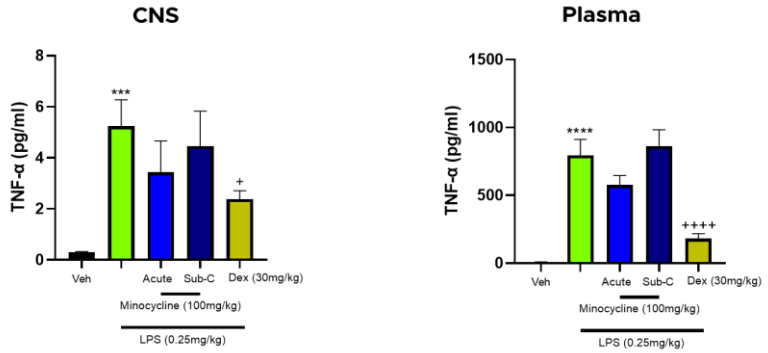


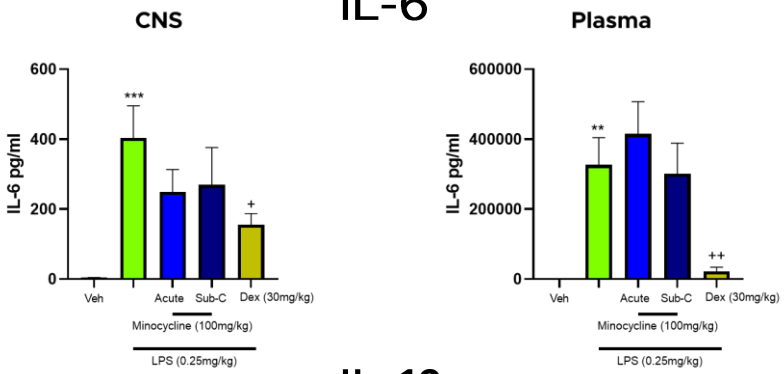
n=4 per group. One-way ANOVA (P<0.05); Fisher's LSD. Values expressed as protein concentration (pg/ml). Data presented as Mean ± SEM.

Results 3

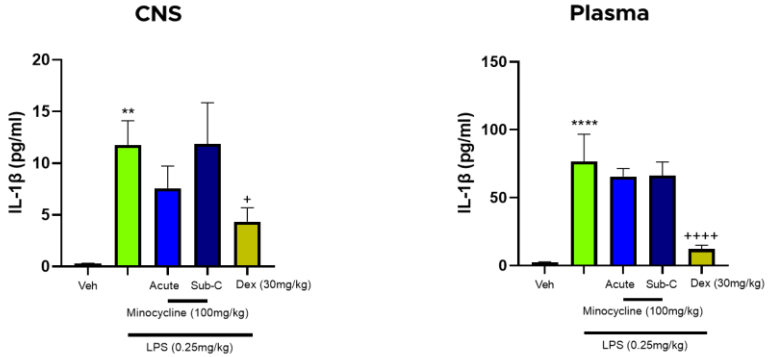
TNF-α



IL-6



IL-1β



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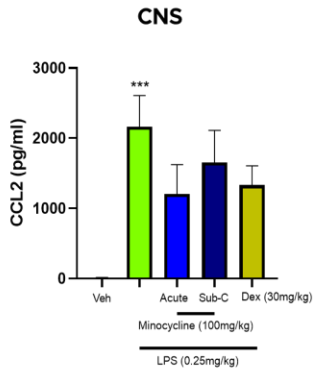

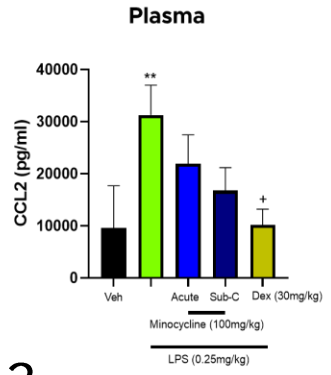

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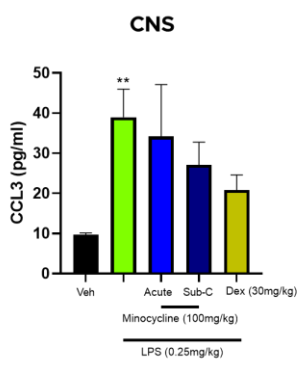

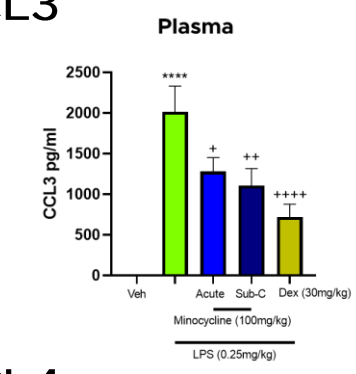

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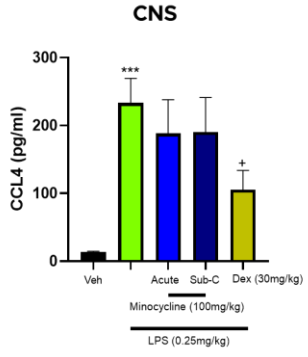

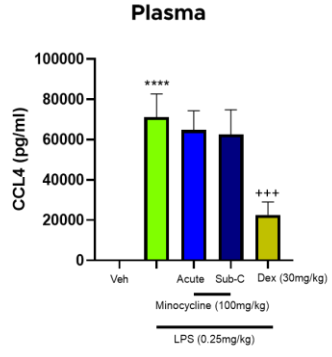

n=9-10 per group. One-way ANOVA (P<0.05); Fisher's LSD. Values expressed as protein concentration (pg/ml). Data presented as Mean ± SEM.

Conclusion

- Both i.p. and i.c.v. LPS administration induced a robust peripheral inflammatory response

- Both i.p. and i.c.v. LPS administration induced a robust central inflammatory response although the specific targets that increased in brain tissue differed between models

- i.p. administration of LPS is sufficient to induce a model of neuroinflammation, responsive to anti-inflammatory drugs, and shows advantages over the i.c.v. model requiring surgical infusion

- Neuroinflammation induced by i.c.v. administration was not contained within the brain at the doses tested here

Funding Sources

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Mouse i.p. and i.c.v. illustrations obtained from SMART – Servier Medical Art